Volume-targeting levels and work of breathing in infants with evolving or established bronchopulmonary dysplasia

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ABSTRACT

Objectives: To assess the work of breathing at different levels of volume targeting in prematurely-born infants with evolving or established bronchopulmonary dysplasia (BPD).

Design: Randomised crossover study

Setting: Tertiary neonatal intensive care unit

Patients: Eighteen infants born at less than thirty-two weeks gestation who remained ventilated at or beyond one week after birth, that is, they had evolving or established BPD.

Interventions: Infants received ventilation at volume targeting levels of 4, 5, 6 and 7ml/kg each for twenty minutes, the levels were delivered in random order. Baseline ventilation (without volume targeting) was delivered for twenty minutes between each epoch of volume-targeting.

Main outcome measures: Pressure-time product of the diaphragm (PTPdi), a measure of the work of breathing, at different levels of volume targeting.

Results: The 18 infants had a median gestational age of 26 (rage 24-30) weeks and were studied at a median of 18 (range 7-60) days. The mean PTPdi was higher at 4ml/kg than at baseline, 5ml/kg, 6ml/kg, and 7ml/kg (all $p \leq 0.001$). The mean PTPdi was higher at 5ml/kg than at 6ml/kg ($p=0.008$) and 7ml/kg ($p<0.001$) and higher at 6ml/kg than 7ml/kg ($p=0.003$). Only at 7ml/kg was the PTPdi significantly lower than at baseline ($p=0.001$).

Conclusions: Only a tidal volume target of 7mls/kg reduced the work of breathing below the baseline and may be more appropriate for infants with evolving or established BPD who remained ventilator dependent at or beyond seven days of age.

INTRODUCTION

In prematurely born infants volume-targeted, as compared to pressure limited ventilation has been shown in systematic reviews to result in reduction in death or BPD, fewer episodes of hypocarbia and reductions in pneumothorax and intracranial haemorrhage.[1, 2] The level of volume targeting varied in the studies included in the systematic reviews. It has been shown that in prematurely-born infants with acute respiratory distress, ventilation with low tidal volumes of 3ml/kg as compared to 5ml/kg increased the level of pro-inflammatory cytokines in tracheal aspirates and prolonged the duration of ventilation.[3] Furthermore, in prematurely born infants with acute respiratory distress,[4] those weaning from ventilation at less than one week of age [5] and in infants born at or near term,[6] volumes of 6ml/kg compared to lower volume targeted levels reduced the work of breathing (WOB). There are, however, no such studies in infants undergoing prolonged ventilation with developing or established bronchopulmonary dysplasia (BPD). Amongst prematurely-born infants ventilated during the first four weeks after birth, tidal volumes increased despite permissive hypercapnia,[7,8] suggesting infants with evolving or established BPD may require larger volume target levels to reduce their WOB than those with acute or resolving RDS. The aim of this study was to test that hypothesis.

METHODS

Infants were eligible for inclusion in the study if they were born at less than thirty-two weeks of gestation and remained ventilated at or beyond one week after birth. We have previously demonstrated all infants who remained ventilator dependent at a week of age developed BPD. In addition, all included infants were to be making spontaneous respiratory efforts during ventilation. Written, informed parental consent was obtained. The study received approval from the South-East Coast - Surrey NHS Research Ethics Committee. The study was registered on the ISRCTN database, number 17041826.

Infants were ventilated using the SLE 5000 or 6000 ventilator (SLE, Croydon UK) with shouldered endotracheal tubes (Smith's Medical, Kent, UK). They each received twenty minutes of volume-targeted ventilation at 4, 5, 6 and 7ml/kg, the order of delivery randomised between infants. They received an initial twenty-minute period of baseline ventilation (without volume targeting) and twenty-minute periods of baseline ventilation between each epoch of VTV. The WOB was recorded for five minutes at the end of each twenty-minute period. The positive end expiratory pressure (PEEP) level and the back-up respiratory rate set on the ventilator were kept the same throughout the study. The fraction of inspired oxygen concentration (FiO_2) was adjusted to maintain oxygen saturations between 92 and 96%.

The WOB was assessed by calculation of the PTPdi. Gastric and oesophageal pressures were measured using a dual pressure transducer tipped catheter (Gaeltec, Dunvegan, Scotland.) Flow was assessed using a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, Scotland), which was inserted between the ventilator circuit and the endotracheal tube and connected to a differential pressure transducer (±2 cm H_2O; MP45; Validyne, Northridge, California, USA). The pneumotachograph had a side port by which airway pressure was measured, this was connected to a pressure transducer (±100 cm H_2O; MP45; Validyne, Northridge, California, USA). Air flow, airway pressure, gastric and oesophageal pressure signals were recorded simultaneously on a personal computer running specially written software (Labview Version 5.0, National Instruments, Austin TX, USA) with 100 Hz analogue-to digital sampling (16 bit DAQ card, DAQ 6036E, National Instruments, Austin, Texas, USA). Tidal volume was calculated by digital integration of the flow signal by the software.

Transdiaphragmatic pressure was obtained by subtraction of the gastric pressure from the oesophageal pressure; this was then integrated with time for the inspiratory portion of each breath to give the pressure time product of the diaphragm (PTPdi). For each breath, the beginning and end of inspiration was determined from the flow signal, in order to delineate the inspiratory work of breathing. The mean PTPdi of the first twenty artefact-free breaths in the last five minutes of the recording of each twenty-minute epoch of ventilation was calculated. The WOB results from the four periods of baseline ventilation were averaged. The mean VTe was calculated from the twenty breaths in each epoch and the total expiratory minute volume (MVe) was calculated by multiplying the mean VTe by the respiratory rate.

Statistics

Data were assessed for normality using the Shapiro-Wilk test. A one-way repeated measures ANOVA was used to assess for differences between the different levels of volume targeting. For some variables, assumptions of sphericity were violated, therefore Greenhouse-Geisser correction was applied where necessary. Bonferroni adjustment was used for post-hoc comparisons. Statistical analysis was performed using IBM SPSS Statistcs 14.

Sample Size

Recruitment of eighteen infants allowed detection with 80% power at the 5% significance level a difference equivalent to one standard deviation in the results of PTPdi between the different levels of volume targeting. The standard deviation was derived from results from previous infants with evolving BPD in whom PTPdi had been measured.

RESULTS

Eighteen babies, median gestational age at delivery 26 (range 24 – 30) weeks and median birth weight 814 (range 438 – 1190) grams were studied at a median of 18 days after birth (range 7-60) days. Fifteen infants had received at least one dose of antenatal steroids and all had received postnatal surfactant. When studied, two babies were supported by synchronised intermittent mandatory ventilation and sixteen by assist control ventilation. All of the infants were subsequently diagnosed with bronchopulmonary dysplasia (BPD, oxygen dependency beyond 28 days). Three had mild, six moderate, and eight severe BPD according to the NIH consensus definition.[9] One infant died before 36 weeks corrected gestational age and hence it was not possible to determine BPD severity.

All babies completed the protocol and had work of breathing assessed at each level of volume targeting. At all levels of volume targeting the infants continued to breathe. The mean PTPdi was higher at 4ml/kg than at baseline, 5ml/kg, 6ml/kg, and 7ml/kg ($p<0.001$). The mean PTPdi was higher at 5ml/kg than at 6ml/kg ($p=0.008$) and 7ml/kg ($p<0.001$) and higher at 6ml/kg than 7ml/kg ($p=0.003$). Only at 7ml/kg was the PTPdi significantly lower than at baseline ($p=0.001$). (Figure 1)

The mean Vte was significantly lower at 4ml/kg than at baseline ($p<0.001$) and higher at 6 and 7ml/kg than baseline ($p=0.026$, $p<0.001$) respectively. The PIP was significantly higher at 7ml/kg than at baseline ($p=0.032$) and 6ml/kg ($p=0.044$) and at baseline than 4ml/kg ($p=0.001$) and 5ml/kg ($p=0.002$) (Table 1). The spontaneous respiratory rate of the infants was significantly higher at 4ml/kg than at baseline ($p=0.049$) and at 4ml/kg and 5ml/kg than at 7ml/kg ($p<0.001$, $p=0.038$) respectively (Table 1). There were no significant differences between the MVe or the FiO_2 at different levels of volume targeting.

DISCUSSION

We have demonstrated that in infants with evolving or established BPD, only at 7ml/kg was the work of breathing significantly reduced from that during pressure-limited ventilation. It has been demonstrated that infants that remain ventilated develop higher tidal volume requirements despite permissive hypercapnia.[7] This likely reflects that infants undergoing prolonged ventilation have an increased dead space.[10] Our findings are important as we have identified a volume targeted level associated with the lowest level of WOB. In the Cochrane review of pressure limited versus volume targeted ventilation, it is stated that currently there is little evidence regarding the appropriate tidal volume target in prematurely born neonates (including those with established BPD).[11]

There were no significant differences in the minute ventilation between the different levels of volume targeting. As the level of volume targeting increased the infants' respiratory rates decreased. Those data suggest that the infants altered their respiratory rates to maintain a relatively constant minute ventilation at different levels of volume targeting to maintain blood gas homeostasis.

In an international survey of volume targeted ventilation, many units reported reluctance to use tidal volumes greater than 6ml/kg for babies with established BPD who remained ventilator-dependent.[12] It is unclear what this upper limit of target volume is based upon. It is perhaps influenced by evidence from adults with acute respiratory distress syndrome in whom ventilation with 6ml/kg rather than 12ml/kg was associated with reduction in mortality.[13] It should be noted that in preterm infants breathing spontaneously on continuous positive airways pressure after delivery, during crying or grunting the median tidal volume recorded exceeded 7ml/kg, thus suggesting that such a tidal volume may be within the normal range.[14] Whilst it is clear from surveys of practice that infants do cope on lower

targeted tidal volumes, it is likely that they are persistently working harder to breathe and, therefore, growth may be impaired. PTPdi is closely related to the oxygen cost of breathing and it has previously been demonstrated that growth failure in infants with BPD is closely related to oxygen consumption. Thus an increased WOB may be detrimental in terms of adequate growth.[15]

At the highest level of volume targeting the respiratory rate of the infants was a mean of 44 bpm compared to 61 bpm at the lowest level of volume targeting. This indicates that there may have been some suppression of the infants' respiratory drive. All of the infants continued to breathe at the highest volume targeted level and thus their respiratory drive was not completely suppressed. Nevertheless, this highlights the importance of when identifying the appropriate level of targeted tidal volume for an individual, not only by assessing their work of breathing by degree of recession and changes in oxygen requirement, but also determining whether they are continuing to breathe.

There are strengths and some limitations to our study. All the infants were subsequently diagnosed with BPD. The infants were examined at all of the four tidal volumes and hence acted as their own controls. Each level of VTV was compared to the baseline level (ie without VTV) which was the average of the four baseline readings. The VTV levels were given in a random order. We used the pressure-time product of the diaphragm as our outcome measure as it is a measure of diaphragmatic metabolic work. Other techniques such as thoracoabdominal asynchrony instead give an indirect measurement of respiratory muscle function. In a future study, it would be useful to also determine the effect of different levels of volume targeting on transcutaneous carbon dioxide levels. This was a crossover study, hence we cannot comment on whether different tidal volumes affected long term outcome.

In conclusion, we have demonstrated that a volume targeted level of 7mls/kg compared to lower volume targeted levels or no volume targeting reduced the WOB in preterm infants with evolving or established bronchopulmonary dysplasia. We have described above that an increased WOB may be detrimental in terms of adequate growth. We would, therefore, recommend a trial of a volume targeted level of 7ml/kg in infants with evolving or established BPD.

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Competing interests: Professor Greenough has held grants from various ventilator manufacturers. Professor Greenough has received honoraria for giving lectures and advising various ventilator manufacturers. Professor Greenough is currently receiving a non conditional educational grant from SLE.

Contributor statement: AG and KA designed the study, KH collected the data, KH, TD and AG were involved in the analysis of the results. All authors were involved in the production of the manuscript and approved the final version.

What is already known on this topic:

- Volume-targeted ventilation compared to pressure-limited ventilation improves outcomes in prematurely-born infants.
- Target tidal volumes of 6ml/kg compared to lower levels reduced the work of breathing in preterm infants with respiratory distress or during weaning.
- Prematurely-born infants undergoing prolonged ventilation may need higher tidal volumes despite permissive hypercapnia

What this study adds

- The work of breathing in infants with evolving or established bronchopulmonary dysplasia (BPD) was assessed at different levels of volume targeting and no volume targeting.
- A volume target of 7mls/kg compared to 4, 5, 6 and no volume-targeting reduced the work of breathing in infants with evolving or established BPD.
- As the volume target level was increased the spontaneous respiratory rate decreased, hence there were no significant differences in minute volume.

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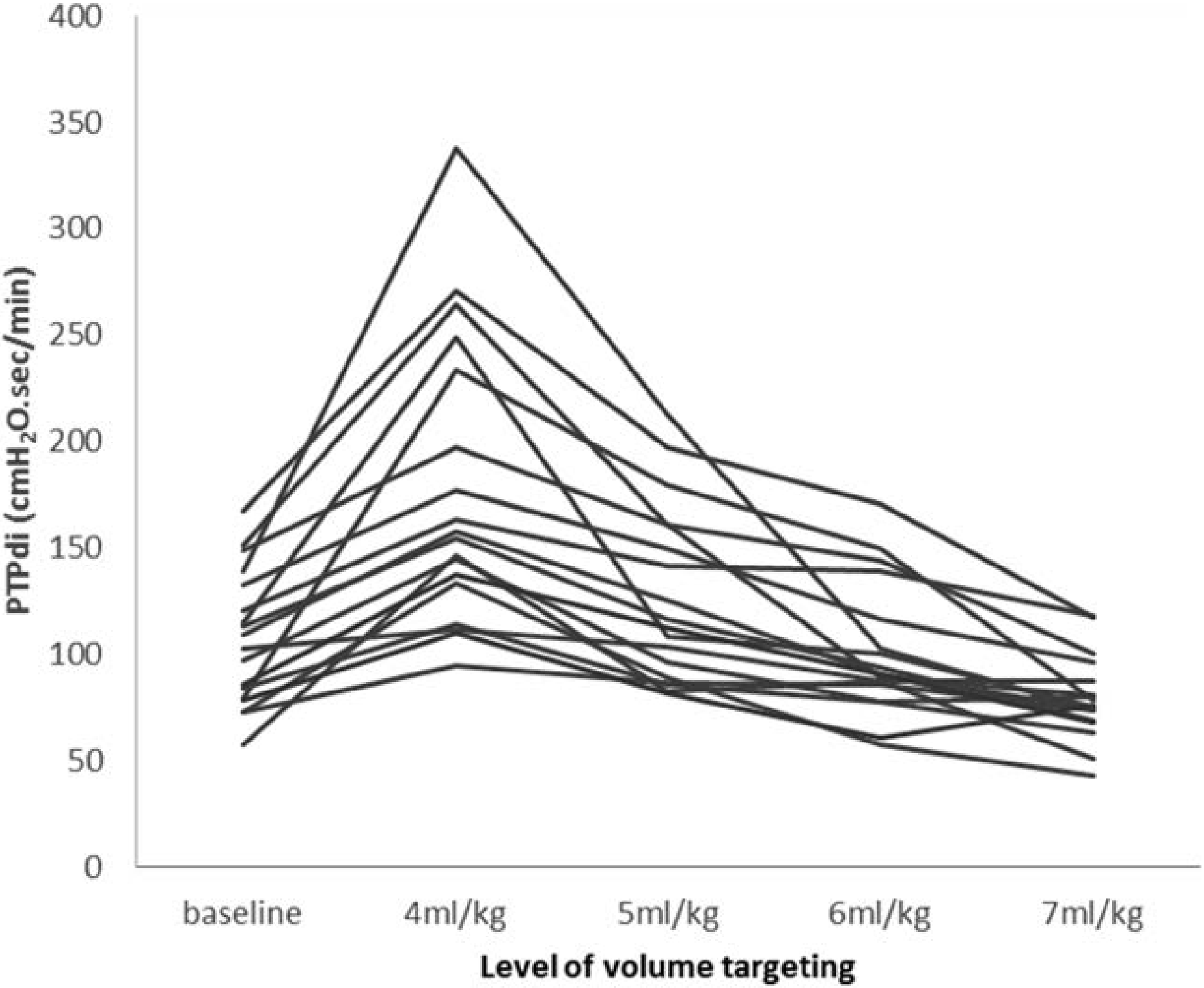
Table 1: Results at different levels of volume targeting and at baseline.

Results are given as the mean (standard deviation).

	baseline	4ml/kg	5ml/kg	6ml/kg	7ml/kg
PTPdi (cmH_2O.sec/min)	106 (31)	177 (67)	127 (41)	101 (31)	78 (20)
VTe (ml/kg)	5.8 (0.6)	4.7 (0.4)	5.3 (0.4)	6.3 (0.4)	7.0 (0.5)
PIP (cmH_2O)	19.7 (3.7)	12.6 (3.1)	15.5 (4.1)	19.4 (4.4)	24.3 (3.8)
Spontaneous respiratory rate (breaths/minute)	54 (10)	61 (10)	56 (15)	51 (16)	44 (9)
MVe (ml/kg/min)	319 (71)	286 (46)	297 (88)	330 (109)	313 (68)
FiO_2	35 (10)	38 (12)	35 (10)	34 (10)	34 (10)

FIGURE LEGEND

Figure 1: PTPdi at baseline (no volume targeting) and at different levels of volume targeting. Results for each individual are shown by linked data points.


400
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PTPdi (cmH2O.sec/min)
baseline
4ml/kg
5ml/kg
6ml/kg
7ml/kg
Level of volume targeting